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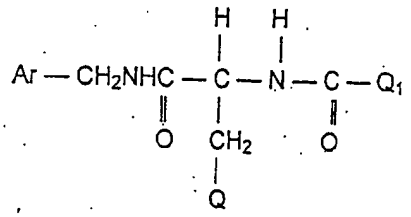
(54) **Novel use of a peptide class of compound for treating allodynia or other different types of chronic or phantom pain**

(57) The present invention concerns the novel use of compounds of the Formula I:



(Formula I)

for treating allodynia as major and unique pain symptom independent of the nature of an underlying disease, but that is often related to neuropathic pain or other different types of chronic or phantom pain.

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Description

Background of the invention

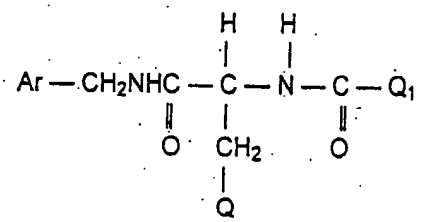
[0001] The present invention relates to the novel use of harkoseride and its derivatives for the preparation of pharmaceutical compositions useful for the treatment of allodynia as a major and unique pain symptom independent of the nature of an underlying disease, but that is often related to neuropathic pain, or other different types of chronic or phantom pain.

[0002] The compounds of the invention are known agents useful in antiseizure therapy for central nervous system disorders such as epilepsy, stroke and cerebral ischemia.

[0003] The instant invention concerns the novel use of a compound of Formula I below for the preparation of pharmaceutical compositions useful for the treatment of pain, particularly for the treatment of chronic pain disorders and especially for the treatment of allodynia as a major and unique pain symptom independent of the nature of an underlying disease, but that is often related to neuropathic pain conditions , or other different types of chronic or phantom pain and tinnitus aureum.

According to the invention compounds are those of Formula I

[0004]



(Formula I)

or a pharmaceutically acceptable salt thereof wherein

[0005] Ar is phenyl which is unsubstituted or substituted with at least one halo group;

[0006] Q is lower alkoxy containing 1-3 carbon atoms and Q_1 is methyl;

diastereomers and enantiomers of compounds of Formula I are included in the invention.

[0007] Preferred compounds of the invention are those according to Formula I in which the compounds are an (R), (S), or (R,S) isomer.

[0008] The most preferred compound of the invention is (R)-2-Acetamido-N-benzyl-3-methoxypropionamide or its pharmaceutically acceptable salt thereof.

[0009] Pain is a subjective experience and the perception of pain is performed in particular parts of the central nervous system.

[0010] Usually noxious (peripheral) stimuli are transmitted to the Central Nervous System (CNS) beforehand, but pain is not always associated with nociception.

[0011] A broad variety of different types of clinical pain exists, that are derived from different underlying pathophysiological mechanisms and that will need different treatment approaches.

[0012] The perception of pain may be characterized by three major types of clinical pain:

- acute pain
- chronic pain
- neuropathic pain

[0013] Acute clinical pain typically results from inflammation or soft tissue injury. This type of pain is adaptive and has the biologically relevant function of warning and enabling healing and repair of an already damaged body part to occur undisturbed. A protective function is achieved by making the injured/inflamed area and surrounding tissue hypersensitive to all stimuli so that contact with any external stimulus is avoided. The neuronal mechanisms underlying this type of clinical pain are fairly well understood and pharmacological control of acute clinical pain is available and effective by means of e.g. Non-Steroidal AntiInflammatory Drugs (NSAIDs) up to opioids depending on type and extension of the sensation.

[0014] Chronic clinical pain appears as sustained sensory abnormalities resulting from an ongoing peripheral pa-

thology such as cancer of chronic inflammation (e.g. arthritis) or it can be independent of the initiating triggers. The latter being maladaptive, offering no survival advantage and very often no effective treatment is available.

[0015] Neuropathic pain is caused by injury or infection of peripheral sensory nerves. It includes, but is not limited to pain from peripheral nerve trauma, herpes virus infection, diabetes mellitus, causalgia, plexus avulsion, neuroma, limb amputation, and vasculitis. Neuropathic pain is also caused by nerve damage from chronic alcoholism, human immunodeficiency virus infection, hypothyroidism, uremia, or vitamin deficiencies. Neuropathic pain includes, but is not limited to pain caused by nerve injury such as, for example, the pain diabetics suffer from.

[0016] Neuropathic pain shows two different pathophysiological mechanisms which have to be considered:

First, enhanced activity of afferent nociceptive neurons following sensitisation of (sleeping) neurons (e.g., inflammatory pain, cancer pain, headache, lower back pain, visceral pain, migraine) with the primary afferent nociceptive neuron remaining intact, though the receptor activity is changed and reduced thresholds, increase of firing rates and starting of or increase of spontaneous activity are typically found.

Second, ectopic activity of afferent nociceptive neurons following lesions of its axons (e.g., peripheral and central neuropathic pain), with the primary afferent neuron being damaged. This leads to irreversible peripheral and central biochemical, morphological and functional changes. Therefore, (peripheral) neuropathy is broadly defined as a disease of the (peripheral) nervous system.

[0017] There are several causes of human neuropathy with considerable variability in symptoms and neurological deficits. Painful neuropathies are defined as neurological disorders characterised by persistence of pain and hypersensitivity in a body region, of which the sensory innervation has been damaged, but damage to sensory nerves does not always produce neuropathic pain, usually loss of sensation rather than hypersensitivity or pain are observed.

[0018] Specific somatosensory disorders are referred to as allodynia (innocuous somatosensory stimulation evokes abnormal intense pain sensation with an explosive, radiating character often outlasting stimulus duration like a trigger), hyperalgesia (noxious stimulation evokes more intense and prolonged pain sensations), paresthesia (spontaneous aversive but nonpainful sensations, described as tingling or "pins and needles"), dysesthesia (evoked as well as spontaneous abnormal sensations).

[0019] Several key events are agreed in as common pathophysiological events of abnormal pain states particularely following peripheral nerve injury. Thus, high frequency spontaneous discharge from ectopic site is followed by an increased responsiveness of dorsal horn neurons and expansion of the receptive field, often defined as central sensitisation.

[0020] Common analgesics like opioids and non-steroidal anti-inflammatory drugs (NSAIDs) improve only insufficiently chronic abnormal pain syndromes. In the search for alternative treatment regimes to produce satisfactory and sustained pain relief, corticosteroids, conduction blockade, glycerol, antidepressants, local anesthetics, gangliosids and electrostimulation have been tried, but mainly anti-convulsants have been found useful against various types of neuropathic pain conditions, but appear to be most effective in cases of paroxysmal, lancinating events, e.g. trigeminal neuralgia.

[0021] If general overactivity and unleaded low threshold activation of sensory neurons is considered as one of the main syndromes of neuropathy and neuropathic pain sensation with a marked mechanoallodynia as the most disabling clinical sympton, selective inhibition of this pathophysiological event instead of general inhibition of high threshold noxious stimuli (by e.g. local anesthetics) of the normal sensory nociception provides clear advantages.

[0022] The conditions listed above are known to be poorly treated by currently marketed analgesics such as narcotics or nonsteroidal anti-inflammatory drugs (NSAID's) due to insufficient efficacy or limiting side effects.

[0023] It is an object of this invention to provide a novel use of compounds according to the aforementioned Formula I and its derivatives for the preparation of pharmaceutical compositions useful for the treatment of allodynia as a major and unique pain symptom independent of the nature of an underlying disease, but that is often related to neuropathic pain, or other different types of chronic or phantom pain.

[0024] Particularly it is an object of this invention to provide a novel use of harkoseride for the preparation of pharmaceutical compositions useful for the treatment of allodynia as a major and unique pain symptom independent of the nature of an underlying disease, but that is often related to neuropathic pain, or other different types of chronic or phantom pain.

[0025] Harkoseride, which chemical name is (R)-2-Acetamido-N-benzyl-3-methoxypropion-amide is one derivative selected of the group of specific amino acid derivatives.

[0026] This group of substances is disclosed in US 5,378,729; US 5,654,301 and 5,773,475. They show activity for the treatment of epilepsy and stroke. But there is no disclosure in the above references to make obvious the present invention.

[0027] The compounds of the present invention may form pharmaceutically acceptable salts with both organic and

inorganic acids or bases.

[0028] For example, the acid addition salts of the basic compounds are prepared either by dissolving the free base in aqueous or aqueous alcohol solution or other suitable solvents containing the appropriate acid and isolating the salt by evaporating the solution.

[0029] Examples of pharmaceutically acceptable salts are hydrochlorides, hydrobromides, hydrosulfates, etc. as well as sodium, potassium, and magnesium, etc. salts.

[0030] The compounds of the present invention can contain one or several assymmetric carbon atoms. The invention includes the individual diastereomers or enantiomers, and the mixtures thereof. The individual diastereomers or enantiomers may be prepared or isolated by methods already well-knwon in the art.

[0031] According to the invention it is preferred that the compounds are in the (R)-configuration. Most preferred is the compound (R)-2-Acetamido-N-benzyl-3-methoxypropionamide.

[0032] The compounds of this invention may be synthesized as disclosed in the documents U.S. P 5,378,729; U.S. P 5,654,301 and U.S. P 5,773,475.

[0033] The compounds made by the synthetic methods can be used as pharmaceutical compositions as agent in the treatment of pain when an effective amount of a compound of the Formula I, together with a pharmaceutically acceptable carrier is used. The pharmaceutical can be used in a method for treating such disorders in mammals, including human, suffering therefrom by administering to such mammals an effective amount of the compounds described above in unit dosage form.

[0034] The pharmaceutical compound, made in accordance with the present invention, can be prepared and administered in a wide variety of dosage forms by either oral or parenteral routes of administration. For example, these pharmaceutical compositions can be made in inert, pharmaceutically acceptable carriers which are either solid or liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets, and suppositories. Other solid and liquid form preparations could be made in accordance with known methods of the art and administered by the oral route in an appropriate formulation, or by a parenteral route such as intravenous, intramuscular, or subcutaneous injection as a liquid formulation.

[0035] The quantity of active compound in a unit dose of preparation may be varied or adjusted from 1 mg to about 300 mg/kg daily, based on an average 70 kg-patient. A daily dose range of about 1 mg to about 50 mg/kg is preferred. The dosages, however, may be varied depending upon the requirement with a patient, the severity of the condition being treated, and the compound being employed. Determination of the proper dosage for particular situations is within the skill of the art.

[0036] The following working examples selected from specific animal models show the anti-neuropathic pain activity of Harkoseride and its derivatives in general and the antiallodynia efficay of Harkoseride and its derivatives in particular.

1. Example 1:

Formalin test, rat

[0037] Significant and dose dependent efficacy of Harkoseride could be demonstrated in the late phase of the rat formalin test.

[0038] The formalin test is a chemically-induced tonic pain model in which biphasic changes of nociceptive behaviour are assessed and spinal/supraspinal plasticity of nociception is considered as a molecular basis for neuropathic pain particularly during the second (=late) phase of the test, during which most clinically used drugs against neuropathic pain are active. These features have resulted in the formalin test being accepted as a valid model of persistent clinical pain.

[0039] The compound was tested for anti-nociceptive properties by use of the weighted behavioural scoring method: Freely moving animals underwent observational assessment of the position of the left hind paw according to a rating score scaled 0-3 before and 10, 20, 30 and 40 min after injection of 0.05 ml of sterile 2.5% formalin under the skin on the dorsal surface of the paw. Harkoseride, administered i.p. just prior to formalin injection produced dose dependant reduction of the formalin-induced tonic inflammatory nociceptive behaviour as shown in table 1 (weighted pain scores ± SEM, n=11-12/group).

Table 1: Weighted pain score, formalin test, rat

		Time After Injection of formalin and SPM 927				
Dose [mg/kg]	No. of Animals	BASELINE	10 MIN	20 MIN	30 MIN	40 MIN
0	11	0.00 ± 0.00	0.30 ± 0.16	0.93 ± 0.21	1.84 ± 0.19	2.10 ± 0.24
5	12	0.01 ± 0.01	0.31 ± 0.11	0.78 ± 0.23	1.47 ± 0.20	1.46 ± 0.19*
10	11	0.00 ± 0.00	0.42 ± 0.17	0.33 ± 0.16*	1.02 ± 0.27*	1.05 ± 0.19*
20	12	0.00 ± 0.00	0.48 ± 0.18	0.57 ± 0.14	0.78 ± 0.18*	1.02 ± 0.24*
40	12	0.00 ± 0.00	0.12 ± 0.05	0.10 ± 0.04*	0.09 ± 0.06*	0.12 ± 0.06*

* = Significant difference from vehicle (ANOVA corrected for multiple comparisons

$p \leq 0.05$.

[0040] The term ANOVA stands for Analysis of Variance.

[0041] These results support and confirm the hypothesised anti-neuropathic pain activity of the compound.

[0042] Data reported here support and give the necessary scientific basis for the activity observed earlier in the writhing test and the mouse formalin test. The former data being limited due to the fact that the writhing test is considered a very unspecific test with some tonic chemically-induced nociceptive aspects that usually gives positive results for all psychoactive drug muscle relaxants etc. therefore not being specific enough to claim specific activity. In addition, the former results obtained in the mouse formalin test, lacks clear evidence of dose relationship and therefore specificity of the observed effects for harkoseride. Furthermore, the only and highest dose giving significant effects in the firts investigation already was found to be celarly toxic. As the toxic effects included changes in behavior,these drug-related changes cannot be claimed as antinociceptive any longer.

[0043] Therefore, only the newly reported data provided here can be considered an in vivo proven antinociceptive effect of harkoseride, with dose dependency serving as measure of specificity and improvement of antinociceptive behavior as being unrelated to toxic effects. Example 2:

Chronic constriction injury (CCI, Bennett-model)

[0044] The effectiveness of Harkoseride in reducing spontaneous chronic pain, mechanical allodynia, and thermal hyperalgesia was tested using the chronic constriction injury (CCI) model of peripheral neuropathy, one of the best characterised in vivo animal models used to study chronic pain due to peripheral nerve injury. In this model, loose ligatures are placed around the sciatic nerve, which produces axonal swelling and a partial deafferentation manifested as a significant but incomplete loss of axons in the distal portion of the peripheral nerve. One of the prominent behaviours seen following sciatic nerve ligation is the appearance of hind paw guarding, thought to be an indication of an ongoing spontaneous chronic pain. Support for this idea is derived from reports of increased spinal cord neural activity, and increased spontaneous neuronal discharge in spinothalamic tract neurons and in the ventrobasal thalamus in the absence of overt peripheral stimulation. In addition to the appearance of spontaneous pain behaviours, several abnormalities in stimulus evoked pain occur as a result of CCI, including thermal hyperalgesia and mechanical allodynia. The development of these abnormal stimulus-evoked pains has also been reported as occurring in areas outside the territory of the damaged nerve, areas innervated by uninjured nerves.

[0045] Behavioural tests for spontaneous pain, thermal hyperalgesia, and mechanical allodynia were conducted to evaluate different components of neuropathic pain. Baseline data for each test was collected prior to any experimental procedure; in addition, all animals were tested for the development of chronic pain behaviours 13-25 days after CCI surgery 1 day prior to the day of vehicle (0.04 ml sterile water /10 g body weight) or drug administration and after vehicle/drug administration. The sequence of the tests was (1) spontaneous pain-related behaviour (2) mechanical allodynia, (3) thermal hyperalgesia in order to minimise the influence of one test on the result of the next. The testing

procedures and results are presented separately for each aspect of chronic pain. Either 0 (vehicle, 0.04 ml/10g body weight), 5, 10, 20 or 40 mg/kg of SPM 927 (n=7-23/group) was administered i.p. 15 minutes before the first behavioural test.

[0046] Spontaneous pain (ongoing pain without an apparent external stimulus) of the ligated paw was assessed for 5 min following a 10 min acclimation period by use of a rating score (weighted behaviour score scaled 0-5).

[0047] Harkoseride did not change the level of spontaneous pain induced by unilateral chronic constriction injury as shown in table 2 (weighted pain scores ± SEM).

Table 2:

Spontaneous nociception, CCI model, rat				
Dose [mg/kg]	**No. of Animals**	**Baseline**	**Post-op**	**Post-op + Drug**
0	23	0 ± 0	1.4 ± 0.15	1.2 ± 0.14
5	9	0 ± 0	2.0 ± 0.10	1.8 ± 0.18
10	20	0.0019 ± 0.0019	1.5 ± 0.10	1.5 ± 0.11
20	8	0 ± 0	1.1 ± 0.17	0.9 ± 0.14
40	10	0.0004 ± 0.0004	1.3 ± 0.12	0.8 ± 0.28

[0048] Thermal hyperalgesia was assessed by means of withdrawal latency in response to radiant heat applied to the subplantar surface of the ligated rat hind paw. As compared to the baseline latency (s), a significant decrease in the (postoperative) latency of foot withdrawal in response to the thermal stimulus was interpreted as indicating the presence of thermal hyperalgesia following chronic constriction injury.

[0049] Harkoseride dose dependently reduced chronic constriction injury-induced thermal hyperalgesia as shown in table 3 [latencies (s) ± SEM]. Significant effects were observed only at the highest doses tested (20 and 40 mg/kg i. p.) with the maximum effect seen already at 20 mg/kg i.p.

Table 3:

Thermal hyperalgesia, CCI model, rat				
0	13	9.8 ± 0.74	7.0 ± 0.29	7.3 ± 0.43
5	7	10.5 ± 0.68	8.1 ± 0.59	9.2 ± 0.98
10	7	9.2 ± 0.68	7.1 ± 0.60	8.1 ± 0.59
20	8	10.0 ± 0.70	7.0 ± 0.56	9.7 ± 0.96*
40	8	8.3 ± 0.57	7.4 ± 0.48	10.2 ± 0.75 *

* = Significant difference from vehicle (ANOVA corrected for multiple comparisons $p \leq 0.05$.

[0050] Mechanical sensitivity and allodynia of the ligated rat hind paw was quantified by brisk foot withdrawal in response to normally innocuous mechanical stimuli as described previously. Responsiveness to mechanical stimuli was tested with a calibrated electronic Von Frey pressure algometer connected to an online computerised data collection system. A significant decrease in the post operative compared to baseline pressure (g/mm^2) necessary to elicit a brisk foot withdrawal in response to this mechanical stimulus is interpreted as mechanical allodynia.

[0051] Harkoseride dose dependently reduced the intensity of mechanical allodynia induced by unilateral nerve ligation as shown in table 4 [pressure (g/mm^2) ± SEM]. Regression analysis showed a positive linear correlation between the dose of Harkoseride and the increase in the amount of force required to produce foot withdrawal

Table 4:

Mechanical allodynia, CCI model, rat				
Dose [mg/kg]	**No. of Animals**	**Baseline**	**Post-op**	**Post-op + Drug**
0	20	41.6 ± 2.20	18.8 ± 2.09	20.2 ± 1.90
5	11	53.6 ± 3.35	16.4 ± 2.56	21.8 ± 2.34

Table 4: (continued)

Mechanical allodynia, CCI model, rat				
Dose [mg/kg]	**No. of Animals**	**Baseline**	**Post-op**	**Post-op + Drug**
10	17	42.9 ± 2.55	21.2 ± 2.13	29.2 ± 2.85 *
20	8	46.1 ± 2.62	24.7 ± 2.78	39.6 ± 3.62 *
40	9	48.4 ± 3.84	23.9 ± 2.23	43.0 ± 5.48*

*= Significant difference from vehicle (ANOVA corrected for multiple comparisons, $p \leq 0.05$).

[0052] These results support and confirm the hypothesised anti-allodynia efficacy of Harkoseride. Furthermore this effect is additionally related to neuropathic pain and therefore supports the potential clinical use of the compound by mimicking the clinical situation of symptom related treatment as close as possible..

[0053] Further proof of specificity of the anti-allodynia effect of harkoseride was given by negative results in the tail flick test excluding typical opioid-like analgesia of the compound. The former data obtained in mice could be repeated and confirmed in a second species, the rat, by additional means of more appropriate choice of the doses tested:

Example 3

Tail flick test, rat

[0054] Harkoseride was additionally tested for potential activity in acute spinal thermal nociception using the tail flick test. In this model of acute thermal spinal/reflex hyperalgesia radiant heat is applied to the animal's tail approximately 2 cm from the tip and time latency for withdrawal reaction is automatically assessed by an algometer, a defined maximal stimulus time prevents tissue damage. This test is widely used as an assay for the anti-nociceptive efficacy of pharmacological agents and is highly predictive of acute analgesic efficacy in humans. Usually pure analgesics of the opioid type are most active; neither adjuvants like amitryptiline nor anti-epileptics nor NSAIDs (non-steroidal anti-inflammatory drugs) are active.

[0055] Results for 20 and 40 mg/kg Harkoseride i.p are shown in table 5 [percent anti-nociception, calculated as [{(post-drug latency) - (pre-drug-latency)}/{(max. latency) - (pre-drug latency)} x 100] ± SEM, n=12/group]. A baseline or pre-drug tail-flick latency was determined by averaging 5 consecutive measurements taken 2 minutes apart. Vehicle (sterile water 0.04ml/10g body weight) or Harkoseride were then administered and tail
flick latencies recorded at 10-minute intervals for the next 60 minutes. Even at doses giving maximum effect in the rat formalin test (see above), Harkoseride had little or no effect on the latency of the tail flick reflex.

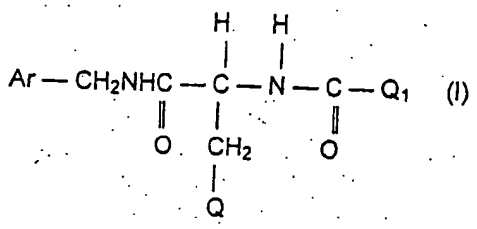
Table 5: Acute thermal hyperalgesia, tail flick, rat

	Anti-nociceptive effect [%] of different doses [mg/kg] of i.p. Harkoseride		
Time after SPM 927[min]	0	20	40
10	-2.1 ± 3.08	5.0 ± 3.94	-1.6 ± 12.82
20	-0.5 ± 3.19	9.7 ± 7.51	-4.3 ± 14.04
30	4.4 ± 4.71	9.7 ± 2.37	-2.3 ± 9.14
40	10.4 ± 5.91	1.7 ± 7.42	-4.4 ± 11.44
50	7.6 ± 4.58	5.4 ± 4.12	0.3 ± 15.50
60	7.4 ± 6.07	8.1 ± 5.20	-5.5 ± 14.11

[0056] Therefore no anti-nociceptive effect of harkoseride was detectable in the tail-flick test, this supports the hypothesised profile of Harkoseride with higly specific anti-allodynia properties and not being active in conditions of acute pain.

Claims

1. Use of a compound having the formula (I)



(I)

wherein

Ar is phenyl which is unsubstituted or substituted with at least one halo group;

Q is lower alkoxy containing 1-3 carbon atoms and Q_1 is methyl or of a pharmaceutically acceptable salt thereof, for the preparation of a pharmaceutical composition for the treatment of allodynia as a major and unique pain symptom independent of the nature of an underlying disease, or other different types of chronic or phantom pain.

2. Use of a compound according to claim 1 wherein Ar is unsubstituted phenyl for the preparation of a pharmaceutical composition for the treatment of allodynia as a major and unique pain symptom independent of the nature of an underlying disease, or other different types of chronic or phantom pain.

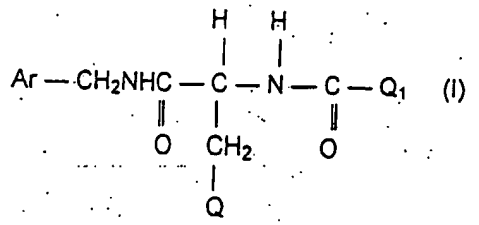
3. Use of a compound according to claims 1 and 2 wherein halo is fluoro for the preparation of a pharmaceutical

composition for the treatment of allodynia as a major and unique pain symptom independent of the nature of an underlying disease, or other different types of chronic or phantom pain.

4. Use of a compound according to claims 1-3 wherein Q is alkoxy containing 1-3 carbon atoms and Ar is unsubstituted phenyl for the preparation of a pharmaceutical composition for the treatment of allodynia as a major and unique pain symptom independent of the nature of an underlying disease, or other different types of chronic or phantom pain.

5. Use of a compound according to claims 1-4 for the preparation of a pharmaceutical composition for the treatment of tinnitus aureum.

6. Use of a compound in the R configuration having the formula (I)



(I)

wherein

Ar is phenyl which is unsubstituted or substituted with at least one halo group;

Q is lower alkoxy containing 1-3 carbon atoms and Q_1 is methyl or of a pharmaceutically acceptable salt thereof, for the preparation of a pharmaceutical composition for the treatment of allodynia as a major and unique pain symptom independent of the nature of an underlying disease, or other different types of chronic or phantom pain.

7. Use of the compound according to claim 6 which is substantially enantiopure for the preparation of a pharmaceutical composition for the treatment of allodynia as a major and unique pain symptom independent of the nature of an underlying disease, or other different types of chronic or phantom pain.

8. Use of a compound according to claims 6 and 7 wherein Ar is unsubstituted phenyl for the preparation of a pharmaceutical composition for the treatment of allodynia as a major and unique pain symptom independent of the nature of an underlying disease, or other different types of chronic or phantom pain.

9. Use of a compound according to claims 6-8 wherein halo is fluoro for the preparation of a pharmaceutical composition for the treatment of allodynia as a major and unique pain symptom independent of the nature of an underlying disease, or other different types of chronic or phantom pain.

10. Use of a compound according to claims 6-9 wherein Q is alkoxy containing 1-3 carbon atoms and Ar is unsubstituted phenyl for the preparation of a pharmaceutical composition for the treatment of allodynia as a major and unique pain symptom independent of the nature of an underlying disease, or other different types of chronic or phantom pain.

11. Use of (R)-2-Acetamido-N-benzyl-3-methoxypropionamide or its pharmaceutically acceptable salt thereof for the preparation of a pharmaceutical composition for the treatment of allodynia as a major and unique pain symptom independent of the nature of an underlying disease, or other different types of chronic or phantom pain.

12. Use of the compound according claim 11 which is substantially enantiopure for the preparation of a pharmaceutical composition for the treatment of allodynia as a major and unique pain symptom independent of the nature of an underlying disease, or other different types of chronic or phantom pain.

13. Use of a compound according to claims 6-12 for the preparation of a pharmaceutical composition for the treatment

of tinnitus aureum.

14. A pharmaceutical composition comprising an antiallodynia effective amount of a compound according to any one of claims 1-13 and a pharmaceutical carrier therefor.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 01 10 7026

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
X	US 5 773 475 A (KOHN HAROLD) 30 June 1998 (1998-06-30)	14	A61K31/165 A61P23/00
A	* see claims 1-11 and col. 8 line 11 *	1-14	
A	WO 96 32100 A (UNIV CALIFORNIA) 17 October 1996 (1996-10-17) * see abstract, claims 11-12 and 20 *	1-14	
A	EUROPEAN JOURNAL OF NEUROLOGY., vol. 7, no. Sup 7, November 2000 (2000-11), pages 3-4, XP001012700 * abstract *	1-14	

TECHNICAL FIELDS SEARCHED (Int.Cl.7)

A61K
A61P

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
MUNICH	5 September 2001	Merckling, V

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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A : technological background
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E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

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EPO FORM 1503 03.82 (P04C01)

ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 01 10 7026

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on
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05-09-2001

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EPO FORM P0459

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82